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Recommendations and metaanalyses

Cardiovascular profile in osteoarthritis: a meta-analysis of cardiovascular events and risk factors

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ABSTRACT

Introduction: Higher cardiovascular risk found in rheumatoid arthritis or psoriatic arthritis is largely due to systemic inflammation. In osteoarthritis (OA), occurrence of systemic inflammation has already been sometimes reported, but the possible association between OA and increased cardiovascular risk remains unclear. In this meta-analysis, we aimed to assess the incidences of myocardial infarction (MI) and stroke, and the cardiovascular risk factors in OA patients.

Methods: We searched PubMed, EMBase, and the Cochrane Library to find references of interest up to June 2018. MI and stroke incidence were calculated using meta-proportion analysis. Differences in cardiovascular risk factors between OA patients and controls were expressed as standardized mean differences using the inverse of variance method.

Results: The reviewed studies reported 227 MIs in 3550 OA patients (incidence, 7.5%; 95% CI: 3.0–13.8%) and 616 MIs among 12,444 control subjects (incidence, 6.0%; 95% CI: 2.8–10.3%). Meta-analysis of the three longitudinal studies revealed a significantly increased MI risk among OA patients (RR = 1.22; 95% CI: 1.02–1.45). We also found a significantly increased stroke risk in OA patients (RR = 1.43; 95% CI: 1.38–1.48). Concerning cardiovascular risk factors, OA patients exhibited a pro-atherogenic lipid and glycemic profile including high levels of fasting glucose, total cholesterol, and LDL cholesterol and a high body mass index. Concerning atherosclerosis markers, OA patients exhibited a higher risk of metabolic syndrome, and increased pulse wave velocity.

Conclusion: Our meta-analysis results revealed higher cardiovascular risk in OA patients. This highlights the importance of cardiovascular risk factor management in OA.

1. Introduction

The risk of cardiovascular disease (CVD) is clearly increased in patients with rheumatic diseases, especially rheumatoid arthritis (RA) and spondyloarthritis [1–8]. This higher cardiovascular risk is related to a pro-atherogenic profile that includes dyslipidemia, as well as to systemic inflammation [9–11]. The rheumatic disease osteoarthritis (OA) has been already reported in some studies to be an inflammatory disease, but to a lesser extent than RA [12,13]. It is presently unclear whether OA is also associated with elevated cardiovascular risk.

Data regarding the cardiovascular risk in OA are scarce and sometimes contradictory. Veronese et al. recently concluded that OA, especially hand OA in women, is associated with a higher risk of CVD development [14]. In contrast, Hoeven et al. found that OA patients showed no increased risk of CVD, and postulated that the previously reported relation between OA and CVD was related to disability in OA [15]. The presently available evidence is insufficient and the number of published studies assessing cardiovacsular risk in OA is lacking to draw strong conclusions.

Here we performed a meta-analysis to increase the statistical power and accuracy of the available data regarding OA and CVD. Our aims were to provide a more accurate assessment of cardiovascular events (myocardial infarction and stroke) in patients with OA, and to compare cardiovascular risk profiles between OA patients and control subjects.

2. Methods

2.1. Literature search

We searched PubMed, EMBase, and the Cochrane Central Register of Controlled Trials to identify all reports of interest published in English or French up to June 19th, 2018. The following search

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terms were used in PubMed: "osteoarthritis[tiab] AND (cardiovascular[tiab] OR myocardial[tiab] OR stroke[tiab] OR intima[tiab] OR lipid [tiab] OR endothelial[tiab])". We did not used any limits to obtain a maximum of references that were thereafter included in analysis or excluded according to the reasons explained in the section "Trail selection". We also performed a manual search of the references of identified articles. Finally, we collected data from the electronic abstract databases of the annual scientific meetings of the French Society of Rheumatology congress, the European League Against Rheumatism (EULAR) congress, and the American College of Rheumatology from 2007–2018 using the following terms: "cardiovascular" OR "lipid" OR "intima" OR "myocardial infarction" OR "stroke" AND "osteoarthritis". We included all observational studies monitoring cardiovascular events, such as myocardial infarction or stroke, and all case-control studies considering cardiovascular risk factors (blood pressure, glycemia, metabolic syndrome, BMI, lipid profile, intima media thickness, and waist circumference) in OA patients and controls.

2.2. Trial selection

One author (SM) identified potentially relevant articles by reading the title, keywords, and abstract first. After this first step of selection, he read the full-text article. The exclusion criteria were commentary, meta-analysis or discussion papers, case reports and studies including fewer than five patients, lack of data about CV risk factors or CVDs, not OA patients, full text not available, and data not usable for statistical analysis (i.e., lacking SD or interquartile range). Duplicate studies were excluded. We defined duplicate studies as: first, studies with the same first author and the same reference in databases; second, studies with the same first author and the same number of patients and the same results and third, studies with the same first author with term such as "ongoing" or "preliminary" studies. In the same study, there may be different groups of OA patients (2 cohorts for example in study of Inoue et al: one for men and another one for women). In this case, the study was included twice: one time for hand OA and one time for knee OA.

Some studies met the inclusion criteria but could be excluded because data extracted and available in these references could not be used in analysis. For example, a transversal study can report cardiovascular profile in OA patients but cannot be included because there is no control group to make the comparison.

2.3. Data extraction

Data extraction was performed by one author (SM). From observational studies, we extracted the number of MIs and strokes, fatal or not. From case-control studies, we recorded the recognized CV risk factors: systolic and diastolic blood pressure, smoking status, glycemia, lipid profile, BMI, and the number of patients with metabolic syndrome or hypertension. We also recorded markers of subclinical atherosclerosis, including intima-media thickness and pulse wave velocity [16,17].

2.4. Statistical analysis

Continuous variables were expressed as the weighted mean ± SD. We calculated the MI and stroke incidences, and the metabolic syndrome prevalence by performing meta-analysis of proportions (inverse of variance method). When the duration of follow-up was available, these incidences were expressed in 100 patient-years (pyrs) of exposure. The Mantel-Haenszel procedure was used to determine the risk ratio (RR) of MI, stroke, and metabolic syndrome in OA patients versus controls in case controlled studies. This method provided a common RR estimate and 95% confidence interval (CI). In longitudinal or case/control studies, we extracted data from control group that was sometimes healthy controls and sometimes controls with another disease such as gout or rheumatoid arthritis. Therefore, we calculated incidences or relative risk for control group concerning all control patients, or when it was available, incidence for healthy controls only.

For continuous variables, including CV risk factors and intima-media thickness, differences between OA patients and controls were expressed as the standardized mean difference using the inverse of variance method—with 0.2–0.8 indicating a moderate differences and > 0.8 a large differences. The statistical heterogeneity between results was assessed using I^2, which is easy to interpret and is the most common metric for measuring the magnitude of between-study heterogeneity. I^2 values range between 0–100%, with < 25% typically considered low, 25–50% modest, and > 50% high [18]. Using this statistical method, we generally assumed the presence of heterogeneity when the *P* value of the I^2 test was < 0.05. In cases of heterogeneity, we used random-effects models; otherwise, we used a fixed-effects model. Statistical analyses were conducted using Review Manager Software, version 5.0 (Cochrane).

3. Results

3.1. Eligible studies

Searching the three databases yielded a total of 2367 citations. After reading the title, abstract, and full text, we eliminated all but 37 eligible studies. We identified 42 other references concerning cardiovascular parameters in OA patients, but the data were not suitable for inclusion in the case-control comparison, commonly due to the lack of control group. Two additional eligible studies were identified by searching the abstract databases for case-control comparisons and three others by hand searching (Fig. 1).

We therefore included 42 studies, comprising a total of 24,501,311 patients and 116,124,120 controls. Eleven studies were longitudinal (Haugen, Hsu, Kendzerska, Kluzek, Sheng, Smith, Veronese, Yang) including three without a control group (Damman, Hawker and Siviero). The rest of the 31 studies were case/control studies. Of these 42 studies, 32 included healthy controls, 6 included controls with RA, and one study control subjects with gout. We clarified which studies contributed to what outcomes and gave their references in Table S1 [See the supplementary material associated with this article online].

3.2. CV events

Among the included studies, 434 MIs were reported in a total cohort of 6244 OA patients, representing an incidence of 6.8% (95% CI: 3.9–10.5%). A follow-up duration was found in five longitudinal studies. Incidence of MI in these 5 OA studies was 0.64/100 patient-years. Five studies provided the numbers of MIs in the control group, reporting 616 MIs among 12,444 control subjects, representing an incidence of 6.0% (95% CI: 2.8–10.3%). Incidence of MI in the 4 control studies with a follow-up duration was 0.40/100 pyrs. Among the 562 reported patients with RA, 70 MIs were reported, showing an MI incidence of 9.4% (95% CI: 0.001–34.8%), i.e. 0.82/100 pyrs. In three studies, 11,882 healthy controls experienced 546 MIs, representing an incidence of 4.6% (95% CI: 4.2–5.0%). Incidence of MI in the 2 healthy control studies with a follow-up duration was 0.18/100 pyrs. Meta-analysis of the three longitudinal studies that compared MI occurrence between OA patients (151 of 2683) and controls (546 of 11,882) revealed a significantly increased MI incidence in OA patients compared with controls (RR = 1.22; 95% CI: 1.02–1.45) (Fig. 2).

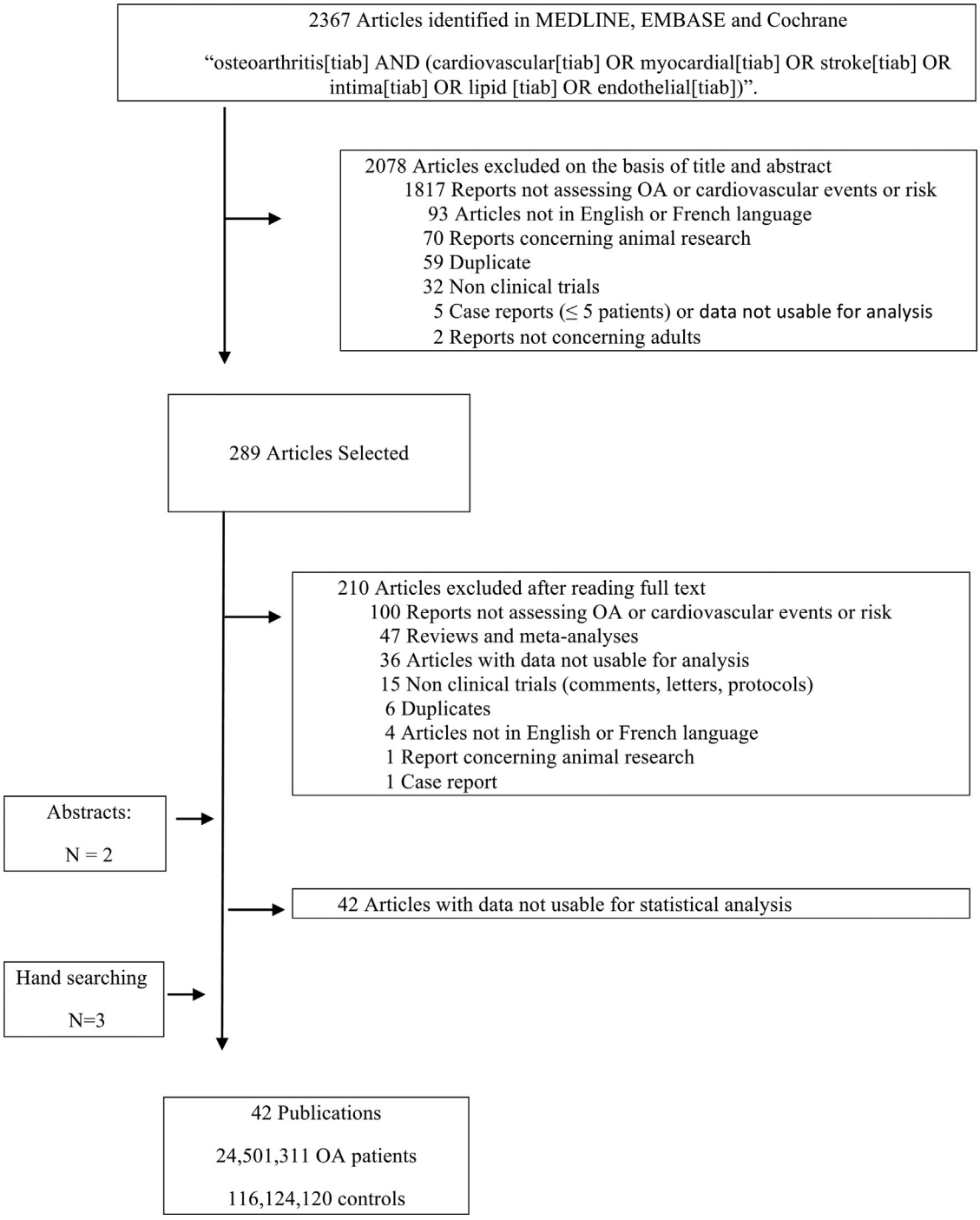

Fig. 1. Flow-chart of the included studies.

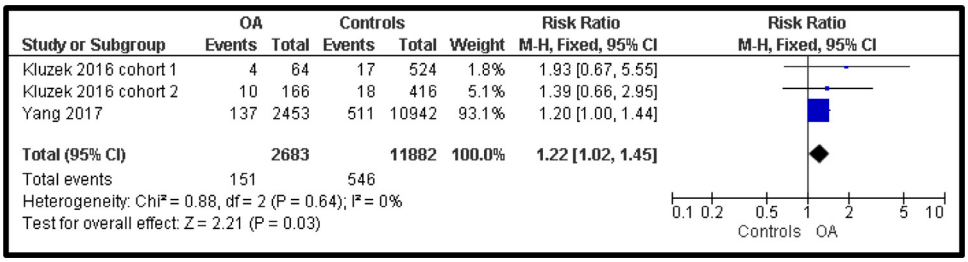

Fig. 2. Comparison of myocardial infarction risk between patients with osteoarthritis (OA) and control subjects.

Table 1
Cardiovascular risk factors in patients with osteoarthritis (OA) and healthy control subjects.

Characteristics	*N* studies *n* participants	OA, weighted mean ± SD	Controls, weighted mean ± SD	Standardized mean difference [95% CI]; fixed or random effects([a])	*P* value	I^2
Glycemia, g/l	*N* = 8 *n* = 11,398	5.67 ± 0.32	5.57 ± 0.29	0.91 [0.46, 1.35][a]	< 0.001	97%
Total cholesterol, mmol/l	*N* = 11 *n* = 47,697	5.74 ± 0.46	5.70 ± 0.49	0.20 [0.09, 0.32][a]	< 0.001	90%
LDL cholesterol, mmol/l	*N* = 9 *n* =12604	3.39 ± 0.40	3.17 ± 0.39	0.60 [0.30, 0.90][a]	< 0.001	96%
HDL cholesterol, mmol/l	*N* = 17 *n* = 49,375	1.40 ± 0.18	1.38 ± 0.18	0.05[−0.07, 0.18][a]	0.41	93%
Triglycerides, mmol/l	*N* = 13 *n* = 47,469	1.44 ± 0.34	1.38 ± 0.37	0.67 [0.40, 0.94][a]	< 0.001	99%
HBA1 C, %	*N* = 3 *n* = 2941	5.30 ± 0.25	5.20 ± 0.26	0.21 [0.14, 0.29]	< 0.001	55%
Systolic BP, mmHg	*N* = 16 *n* = 50,675	129.5 ± 5.7	129.1 ± 5.7	0.41 [0.29, 0.53][a]	< 0.001	93%
Diastolic BP, mmHg	*N* = 12 *n* = 48,769	77.3 ± 3.7	78.5 ± 1.6	0.02[−0.17, 0.20][a]	0.85	97%
BMI, kg/m^2	*N* = 16 *n* = 61,290	26.9 ± 1.3	25.4 ± 0.8	0.30 [0.24, 0.37][a]	< 0.001	79%
Waist circumference, cm	*N* = 6 *n* = 36,745	89.1 ± 1.5	85.2 ± 3.5	0.31 [0.13, 0.48][a]	< 0.001	90%
IMT, cm	*N* = 3 *n* = 5390	0.97 ± 0.10	0.97 ± 0.11	0.29[−3.60, 4.19][a]	0.88	100%
AIx, %	*N* = 2 *n* = 237	25.0 ± 0.6	22.3 ± 1.1	0.28 [0.02, 0.53]	0.03	0%
PWV, mm/s	*N* = 2 *n* = 237	9.3 ± 0.1	8.3 ± 0.3	0.51 [0.25, 0.76]	< 0.001	0%
CRP, mg/l	*N* = 5 *n* = 1159	4.70 ± 3.03	2.85 ± 1.48	0.34 [0.22, 0.46]	< 0.001	11%

LDL: low-density lipoprotein; HDL: high-density lipoprotein; TC: total cholesterol; CI: confidence interval; SD: standard deviation; HBA1C: glycated hemoglobin; BP: blood pressure; BMI: body mass index; IMT: intima media thickness; AIx: augmentation index; PWV: pulse wave velocity, CRP: C-reactive protein.
[a] Statistical method used random effects. No symbol means statistical method used fixed effects.

In seven longitudinal studies (*n* = 52,591 patients), 9894 strokes were reported in OA patients, representing an incidence of 7.1% (95% CI: 2.2–14.5%). Incidence of stroke in the 4 OA studies with a follow-up duration was 1.2/100 pyrs. Four studies reported a total of 7,347 strokes in control subjects (*n* = 55,139), demonstrating an incidence of 5.9% (95% CI: 0.8–15.0%). Incidence of stroke in the 3 controls studies with a follow-up duration was 0.8/100 pyrs. Meta-analysis of the two longitudinal studies comparing stroke occurrence between OA patients (9396 of 46,088) and controls (7324 of 54,577) revealed a significantly increased stroke incidence among OA patients compared with controls (RR = 1.43; 95% CI: 1.38–1.48) (Supplementary data, Figure S1).

3.3. CV risk profile

Among OA patients, the weighted mean age was 62.4 ± 11.7 years, and 61% were women. Approximatively 20% were smokers, and 46% were treated for hypertension. The weighted mean systolic BP was 126.5 ± 12.5 mmHg, and diastolic BP was 75.7 ± 8.7 mmHg. The weighted mean BMI was 30.4 ± 4.3 kg/m^2.

3.4. Comparison of OA patients and healthy controls

Table 1 presents the comparison of cardiovascular risk factors between OA patients and healthy controls. Compared to healthy controls, OA patients showed higher levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, fasting glucose, and glycated hemoglobin. OA patients also showed higher systolic blood pressure, BMI, waist circumference, augmentation index (AIx), pulse wave velocity (PWV), and systemic inflammation compared to healthy control subjects. The risk of metabolic syndrome was two-fold higher in OA patients (RR = 2.08; 95% CI: 1.30–3.34) (Fig. 3). The OA and healthy control groups did not differ with regards to diastolic pressure, high-density lipoprotein (HDL) cholesterol, or intima media thickness (IMT).

3.5. Comparison of OA patients and RA controls

In the six studies comparing OA and RA patients, we found no significant between-group difference in the incidence of MI (76/876 OA patients versus 70/562 RA patients; RR = 1.06; 95% CI: 0.74–1.53) or stroke (33/867 OA patients versus 23/562 RA patients; RR = 1.24; 95% CI: 0.71–2.18). The two groups also did not significantly differ in levels of LDL or HDL cholesterol (Table 2). In contrast, OA patients showed higher levels of total cholesterol and triglycerides compared with RA patients.

4. Discussion

Our meta-analysis results revealed increased risks of MI and stroke among OA patients compared to healthy controls. OA patients also exhibited significantly increased markers of subclinical atherosclerosis, including pulse wave velocity and AIx. The higher cardiovascular risk in OA patients may be due to systemic inflammation characterized by increased C-reactive protein. Patients with OA showed higher CRP levels than healthy controls (4.70 ± 3.03 vs. 2.85 ± 1.48 mg; $P < 0.001$).

The CRP levels in patients with OA corresponded to lower systemic inflammation than found in other rheumatic diseases, such as RA. However, the incidence of cardiovascular events did not significantly differ between RA and OA patients. This may have been because low systemic inflammation is sufficient to generate increased cardiovascular risk. Another possible explanation is the cardiovascular risk profile of the included patients. Among the OA patients, 20% were smokers, and 46% were treated for hypertension. OA patients exhibited a pro-atherogenic lipid profile with

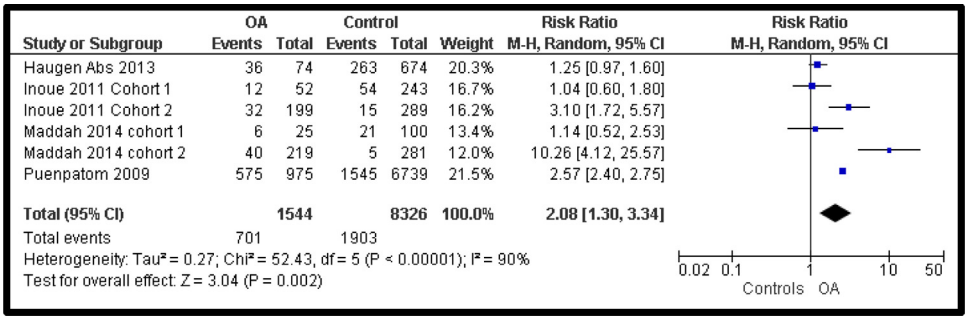

Fig. 3. Comparison of metabolic syndrome risk between patients with osteoarthritis (OA) and control subjects.

Table 2
Comparison of lipid profiles between patients with osteoarthritis (OA) and patients with rheumatoid arthritis (RA).

Characteristics	*N* studies *n* participants	OA, weighted mean ± SD	RA, weighted mean ± SD	Standardized mean difference [95% CI]; fixed or random effects(*)	*P* value	I^2
Total cholesterol, mmol/l	*N* = 4 *n* = 29,321	4.92 ± 0.37	4.90 ± 0.35	0.19 [0.09, 0.28]*	< 0.001	76%
LDL cholesterol, mmol/l	*N* = 3 *n* = 4576	2.76 ± 0.32	2.78 ± 0.27	−0.04 [−0.10, 0.01]	0.14	1%
HDL cholesterol, mmol/l	*N* = 3 *n* = 28,499	1.32 ± 0.10	1.36 ± 0.13	0.25 [−0.15, 0.64]*	0.23	99%
Triglycerides, mmol/l	*N* = 3 *n* = 28,499	1.54 ± 0.20	1.55 ± 0.29	0.09 [0.06, 0.13]	< 0.001	0%

LDL: low-density lipoprotein; HDL: high-density lipoprotein; CI: confidence interval; SD: standard deviation; *: Statistical method used random effects. No symbol means statistical method used fixed effects.

high levels of total cholesterol and LDL cholesterol, and a pro-atherogenic glycemic profile with high levels of fasting glucose and glycated hemoglobin. OA patients had a greater risk of metabolic syndrome and exhibited a larger waist circumference, which is a significant indicator of high cardiovascular risk. Xu et al. reported an increased MI risk in healthy obese patients (BMI > 28 kg/m^2) with metabolic syndrome—a category that corresponds to OA patients [19]. OA patients also showed higher adiponectin and free fatty acids, which are associated with a higher incidence of major cardiovascular events [20–22]. The worse cardiovascular risk profile found in OA patients is the same as reported in atherosclerosis and RA patients, and might be the major explanation for the elevated cardiovascular risk in OA.

Scientific societies now recommend the management of cardiovascular risk in RA patients [23–25]. Despite insufficient implementation of these recommendations [26,27], cardiovascular risk in RA is decreasing [28,29]. In the same way, our present findings indicate that it is important to make OA patients and medical doctors aware of the need to investigate cardiovascular risk factors and to control them when necessary. However, additional studies are needed to clarify the roles of cardiovascular risk factors in OA development. For example, tobacco use is implicated in RA occurrence, but does not seems to play a role in OA development, and was even reported many years ago to be protective [30,31].

Our present study has several limitations. First of all, it could be said that our study doesn't provide new information. Osteoarthritis is recognized to be a "serious" disease associated with increased mortality primarily from cardiovascular disease. In addition, OA is associated with the metabolic syndrome, characterized by hypertension, hyperlipidemia, type 2 diabetes mellitus and hyperuricemia, all independent risk factors for cardiovascular thrombotic disease. Furthermore, persons with symptomatic lower limb OA (hip and/or knee) have reduced physical activity and often use nonsteroidal anti-inflammatory drugs for pain relief; both of these are independent risk factors for cardiovascular thrombotic events. However this manuscript provides a quantitative synthesis of the literature that permit to better appreciate and understand this cardiovascular risk in OA.

Only three studies were included for the comparison of MI incidence, and only one of these studies had a sufficient sample size to draw conclusions ($n = 2453$). Therefore, the fact that the results are driven mainly by one large study is of course a major drawback. However, these few studies are the only source of information available in the literature; therefore, our present findings represent the best presently available knowledge. The interest of our meta-analysis is to make aware of this potential increased cardiovascular risk in OA patients and to convince authors and investigators that other studies are needed to confirm our results. For example, we found that MI risk did not differ between RA and OA patients, but that analysis included only two studies and a small number of patients. Moreover, the cardiovascular risk among RA patients in those two studies was low compared to other studies assessing MI risk in RA, which have reported the relative risk of MI being closer to 1.5 or even 2 [32–34]. Thus, the RA patients in the two analyzed studies may not be perfectly representative of RA patients in general, possibly leading to underestimation of the difference between OA and RA in our study. Another limitation is related to the principle of meta-analysis, in that the reader can only extract the data reported in the published manuscripts. We identified 42 other references involving cardiovascular parameters in OA patients, but none were included because published data were not usable for our analysis, especially because these studies were transversal studies without any control group. Another limitation is related to the publication bias—in that positive studies are more likely to be published than negative studies. We cannot exclude that some investigations have found no significant increase of cardiovascular risk in OA patients, but were never published or even submitted. However, we searched relevant abstracts in European and American rheumatological congresses, and trial registries, such as PROSPERO (international prospective register of systematic reviews), and found no other references.

Overall, our present meta-analysis demonstrated that OA patients seem to have a higher cardiovascular risk compared to healthy controls, and the same cardiovascular risk as RA patients. This could be due to systemic inflammation, but is likely mainly related to cardiovascular risk factors, such as dyslipidemia and metabolic syndrome. OA patients and medical doctors should be aware of the importance of cardiovascular assessment in OA. Recently authors reported the Phenotypic Approach to Osteoarthritis and the role of environmental factors in the pathogenesis of OA. Primary prevention and appropriate management of obesity and metabolic syndrome may delay the development and slow the progression of osteoarthritis [35,36].

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Author contributions

All authors were involved in drafting this article or critically revising it for important intellectual content, and all authors approved the final version to be submitted for publication.

Dr. Mathieu had full access to all of the study data, and takes responsibility for the data integrity and the accuracy of the data analysis.

Study conception and design: Mathieu, Couderc, Tournadre, Soubrier.

Acquisition of data: Mathieu.

Analysis and interpretation of data: Mathieu, Couderc, Tournadre, Soubrier.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2019.06.013.

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